Fluorous-Soluble Metal Chelate for Sensitive Fluorine-19 Magnetic Resonance Imaging Nanoemulsion Probes.

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Public Summary:
Fluorine-19 MRI is an emerging cellular imaging approach, enabling lucid, quantitative "hot-spot" imaging with no background signal. The utility of 19F-MRI to detect inflammation and cell therapy products in vivo could be expanded by improving the intrinsic sensitivity of the probe by molecular design. We describe a metal chelate based on a salicylidene-tris(aminomethyl)ethane core, with solubility in perfluorocarbon (PFC) oils, and a potent accelerator of the 19F longitudinal relaxation time (T1). Shortening T1 can increase the 19F image sensitivity per time and decrease the minimum number of detectable cells. We used the condensation between the tripodal ligand tris-1,1,1-(aminomethyl)ethane and salicylaldehyde to form the salicylidene-tris(aminomethyl)ethane chelating agent (SALTAME). We purified four isomers of SALTAME, elucidated structures using X-ray scattering and NMR, and identified a single isomer with high PFC solubility. Mn^{4+}, Fe^{3+}, Co^{3+}, and Ga^{3+} cations formed stable and separable chelates with SALTAME, but only Fe^{3+} yielded superior T1 shortening with modest line broadening at 3 and 9.4 T. We mixed Fe^{3+} chelate with perfluorooctyl bromide (PFOB) to formulate a stable paramagnetic nanoemulsion imaging probe and assessed its biocompatibility in macrophages in vitro using proliferation, cytotoxicity, and phenotypic cell assays. Signal-to-noise modeling of paramagnetic PFOB shows that sensitivity enhancement of nearly 4-fold is feasible at clinical magnetic field strengths using a 19F spin-density-weighted gradient-echo pulse sequence. We demonstrate the utility of this paramagnetic nanoemulsion as an in vivo MRI probe for detecting inflammation macrophages in mice. Overall, these paramagnetic PFC compounds represent a platform for the development of sensitive 19F probes.

Scientific Abstract:
Fluorine-19 MRI is an emerging cellular imaging approach, enabling lucid, quantitative "hot-spot" imaging with no background signal. The utility of (19)F-MRI to detect inflammation and cell therapy products in vivo could be expanded by improving the intrinsic sensitivity of the probe by molecular design. We describe a metal chelate based on a salicylidene-tris(aminomethyl)ethane core, with solubility in perfluorocarbon (PFC) oils, and a potent accelerator of the (19)F longitudinal relaxation time (T1). Shortening T1 can increase the (19)F image sensitivity per time and decrease the minimum number of detectable cells. We used the condensation between the tripodal ligand tris-1,1,1-(aminomethyl)ethane and salicylaldehyde to form the salicylidene-tris(aminomethyl)ethane chelating agent (SALTAME). We purified four isomers of SALTAME, elucidated structures using X-ray scattering and NMR, and identified a single isomer with high PFC solubility. $Mn(4+)$, $Fe(3+)$, $Co(3+)$, and $Ga(3+)$ cations formed stable and separable chelates with SALTAME, but only $Fe(3+)$ yielded superior T1 shortening with modest line broadening at 3 and 9.4 T. We mixed $Fe(3+)$ chelate with perfluorooctyl bromide (PFOB) to formulate a stable paramagnetic nanoemulsion imaging probe and assessed its biocompatibility in macrophages in vitro using proliferation, cytotoxicity, and phenotypic cell assays. Signal-to-noise modeling of paramagnetic PFOB shows that sensitivity enhancement of nearly 4-fold is feasible at clinical magnetic field strengths using a (19)F spin-density-weighted gradient-echo pulse sequence. We demonstrate the utility of this paramagnetic nanoemulsion as an in vivo MRI probe for detecting inflammation macrophages in mice. Overall, these paramagnetic PFC compounds represent a platform for the development of sensitive (19)F probes.